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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,762	03/19/2004	Yan Qi	A-72186/TAL/DCF	8100

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,762	QI ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☒ Claim(s) *14-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/04, 10/18/05* and 2/15/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of 12/27/05 is entered.

Claims 1-26 are presently pending.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-17 in the reply filed on 12/27/05 is acknowledged.

Claims 18-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/27/05.

Claims 1-17 are presently considered.

Claim Objections

Claims 14-17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claims. See MPEP § 608.01(n). Accordingly, the claims 14-17 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

Claims 1-3, 5-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(i) a method for inhibiting the development of adaptive CTL immunity to allogenic target cells exhibiting cell-surface expressed target cell specific antigens, comprising contacting the target cell with an expression vector comprising a cell-surface expressed CD8-alpha chain transgene, wherein said CD8-alpha chain is expressed on the surface of the cell, and thereby inhibits the subsequent development of adaptive CTL immunity to such cell-expressed antigens;

(ii) a method for specifically inhibiting the development of donor-induced adaptive CTL immunity to allogenic cells in a recipient, comprising transforming the cells of the donor allograft cells with a vector for expressing a CD8-alpha chain on the cell surface prior to transplantation, then transplanting the cells into the recipient, wherein said CD8-alpha chain is expressed on the surface of the cells and inhibits the development of adaptive CTL immunity to such cell-expressed antigens; and

(iii) a method for extending the survival of an allograft in a recipient, comprising similar steps to (ii), does not reasonably provide enablement for inhibiting any immune response, inhibiting immune response to antigens alone, inhibiting xenogenic immune responses, any transformation of the tissues involved *in vivo*, and any form of conditioning cells to express CD8 alpha chains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 4, 10-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claimed subject matter encompasses a method for inhibiting any host immune response to any target cell specific antigen, simply comprising contacting a target cell expressing the antigen with an expression vector encoding a CD8 polypeptide comprising the CD8 alpha-chain, whereby the CD8 is expressed and host immune response is inhibited. Also encompassed is a method for inhibiting all immune responses to donor antigens in a recipient,

comprising conditioning any donor allograft cells having the antigen(s) to express a CD8 comprising the alpha-chain, prior to or contemporaneous with transplantation, wherein the CD8 expression specifically inhibits the recipient alloimmune response to the donor antigens. Also encompassed is a method for extending survival to an allograft, comprsiging similar steps. Also encompassed is a method for inhibiting all immune responses to recipient antigens by donor T cells, comprising conditioning any recipient cells at risk of GVHD to express CD8 comprising the alpha chain, contemporaneous or subsequent to transplantation of the T cells, wherein the CD8 is expressed and inhibits the donor alloimmune response to the recipient antigens. Also encompassed is a method for suppressing GVHD in a recipient, comprising conditioning cells of the recipient at risk of GVHD to express CD8 including the alpha-chain, contemporaneous or subsequent to transplantation, wherein the CD8 is expressed and the GVHD against the recipient cells by the donor T cells is suppressed.

Applicant's examples demonstrate that only that T-cell activation is suppressed, and that no other response is affected. Also, the Examples demonstrate that already activated T-cells cannot be inhibited. Also, the Examples demonstrate that only suppression of antigens expressed on the surface of a cell can be inhibited. Also, the Examples demonstrate that the alpha-chain alone is required for such inhibition of development of activated T-cells.

The specification teaches Applicant's invention is based on the surprising discovery that the veto effect mediated by targeted expression of CD8-alpha can suppress CD4+ as well as CD8+ T cells, thereby inhibiting allogenantigen directed humoral and cellular responses (paragraph 012). The specification further teaches the breadth of alpha-chains required to

practice the invention, expression vectors, delivery of vectors to cells, and formulations of vector compositions.

However, the specification and examples do not demonstrate or make reasonably predictable for inhibiting any immune response, inhibiting immune response to antigens alone, inhibiting xenogenic immune responses, and any form of conditioning cells to express CD8 alpha chains, transforming or conditioning enough recipient cells, to effect the breadth of the methods claimed.

With regard to non-allogenic transplantation of cells *Game et al* (Wien Klin Wochenschr 2001;113:823-38) detailed different types of allogenic and xenogenic rejection (hyperacute, acute, chronic) and underlying mechanisms involving multiple pathways that lead to the failure of allogenic and xenogenic transplantation, and states, "WHILE MAJOR IMPROVEMENTS HAVE BEEN MADE IN THE PREVENTION AND TREATMENT OF HYPERACUTE AND ACUTE TRANSPLANT REJECTION, MOST GRAFTS WILL SUCCUMB TO CHRONIC REJECTION: THIS REFLECTS THE EXTENT OF OUR KNOWLEDGE OF THE MECHANISMS THAT DRIVE THESE PROCESSES", as for xenotransplantation, "NOVEL APPROACHES HAVE OVERCOME SOME EARLY ANTIBODY MEDIATED REJECTION EVENTS BUT THEN REVEAL A HUGE, INTENSE, ADAPTIVE CELLULAR RESPONSE". Hence, other than allogenic transplantation, no other form of transplantation is reasonably predicted to work.

With regard to inhibiting response to antigens alone, it is clear from the specification that such proteins must be expressed on the surface of the cells (EXAMPLES).

With regard to the any immune response, Applicant has not demonstrated how this affects other immune responses, like B-cell responses, and the art does not teach that such expression of the same CD8 will have any effect on these cells.

With regard to forms of conditioning to express CD8 alpha chains, the Art and Applicant's specification only teach one form: transforming the cells with vectors to cause such expression of the CD8 alpha chains on the surface of the cell.

With regard to transforming or conditioning enough recipient cells, or such transformation/conditioning after transplantation, gene therapy generally demonstrates that not enough cells are reasonably predicted to be transformed (note that this must be all cells, as the T-cells migrate and can act anywhere) and express enough protein for a long enough period of time to have an effect. To wit, the field of gene therapy is quite complex and remains an unpredictable art. Verma et al. states that in the past, the Achilles heel of gene therapy was gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2}. These issues remain as current problems in the field of gene therapy. Pfeifer and Verma state that even "though gene therapy holds great promise for the achievement of this task, the transfer of genetic material into higher organisms still remains an enormous technical challenge { Pfeifer and Verma (2001) Annu. Rev. Genomics. Hum. Genet. 2:177-211; pg. 177, pgph 1}. Johnson-Saliba et al. concurs stating that "although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches, especially when non-viral vectors are used, is the poor efficiency of DNA delivery." {Johnson-Saliba et al. (2001) Curr. Drug. Targets 2:371-99;

Abstract}. Such problems with delivery continue to plague the field of gene therapy. Shoji et al. has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based-medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non-toxicity, non-pathogenicity, non-immunogenicity, [and] non-tumorgenicity." {Shoji et al. (2004) Current Pharmaceutical Design 10 :785-796}. The long-standing problems in the field of gene therapy indicate that the results observed by the Applicant's *ex vivo* transformations, are not sufficient to allow a practitioner skilled in the art to predict how to successfully practice the claimed invention as a method of gene therapy, with any nucleic acid sequence encoding all or a part of a CD8 alpha chain, without undue experimentation.

Hence, even though the Artisan is highly skilled in this field, the level of predictability is low, and therefore, the Artisan would have to perform undue experimentation, amounting to inventing Applicant's claimed subject matter himself/herself, to reasonably predict the working embodiments encompassed by the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-14 rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Application No. 2002/0127205 to Edge, et al.

With regard to Claim 1, 5, 6, 7, Edge teaches compositions comprising genetically modified cells which express molecules to inhibit T-cell activation which can be used for transplantation (ABSTRACT). Such transgenically expressed proteins include CD8 (paragraph 0009). Moreover, graft survival can be extended (paragraph 0006) (See Also, Claim 1.)

With regard to Claims 2-3, allogenic subjects are taught (paragraph 0049), as well as conditioning of the donor cells (ABSTRACT).

With regard to claims 7-8, Edge teaches *ex vivo* perfusion of the tissues.

Conclusions

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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